UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,837	06/24/2003	Hua Shi	19603/3921 (CRF D-2944A)	8111

7590 09/12/2007

Nixon Peabody LLP
Clinton Square
P.O. Box 31051
Rochester, NY 14603-1051

EXAMINER	
THOMAS, DAVID C	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
09/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/602,837	Applicant(s) SHI ET AL.	
	Examiner David C. Thomas	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 10 July 2007.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-15 and 18-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-15 and 18-22 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 10, 2007 has been entered. Claims 1, 15, 18 and 19 (amended) and 2-14 and 20-22 (original) will be examined on the merits. Claims 16 and 23-46 were previously canceled and claim 17 is newly canceled.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 2, 4, 7-11 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmidt et al. (U.S. Patent No. 5,792,613).

Schmidt teaches a method of identifying RNA ligands which bind to a target molecule (ligand binding of nucleic acids by shape recognition, column 2, lines 17-22), said method comprising:

preparing, through one or more rounds of amplification and selection, a first pool of RNA ligands that collectively bind more than one target, wherein the first pool of RNA ligands comprises one or more predominate target-binding RNA ligands and one or more non-predominate target-binding RNA ligands (RNA population used as the starting material can be a synthetic RNA library, column 3, lines 26-27; a synthetic RNA library is amplified by PCR for five cycles, starting with a starting library selected to contain strings of randomized nucleotides bounded by promoter sequences, column 9, lines 37-51; one microgram of the amplified material was transcribed with T7 RNA polymerase to produce transcripts that were purified by gel electrophoresis to provide the synthetic RNA library used in aptamer selection, and which represents a starting pool of both predominate and non-predominate target-binding RNA ligands, column 9, line 62 to column 10, line 7);

treating the first pool of RNA ligands under conditions effective to reduce the concentration or eliminate the presence of one or more predominate target-binding RNA ligands from the first pool of RNA ligands (contacting RNA population with both blocking agent and selecting nucleic acid molecule and separating non-complexed RNA from complexed population to enrich for the RNA aptamer of interest, column 2, line 63 to column 3, line 20);

amplifying the RNA ligands in the treated first pool, thereby forming a second pool of RNA ligands that is enriched in one or more non-predominate target-binding RNA ligands of the first pool but not the one or more predominate target-binding RNA ligands thereof (after each round, selected RNA population enriched for RNA aptamer,

is reverse transcribed to cDNA, amplified, and transcribed back to RNA before next round, column 3, lines 28-32); and

identifying from the second pool one or more predominate target-binding RNA ligands that are present in the second pool at a higher concentration than other target-binding RNA ligands (cDNA is sequenced to identify enriched aptamer, column 3, lines 32-36).

With regard to claim 2, Schmidt teaches a method further comprising:

treating the second pool under conditions effective to reduce the concentration or eliminate the presence of one or more predominate target-binding RNA ligands (process is repeated a second round by contacting RNA population with selecting nucleic acid molecule and separating non-complexed RNA from complexed population to enrich for the RNA aptamer of interest, column 3, lines 11-25);

amplifying the RNA ligands in the treated second pool, thereby forming a third pool of RNA ligands that is enriched in one or more non-predominate target-binding RNA ligands of the second pool but not the one or more predominate target-binding RNA ligands thereof (after the first and succeeding rounds, selected RNA population enriched for RNA aptamer of interest, is reverse transcribed to cDNA, amplified, and transcribed back to RNA before next round, column 3, lines 28-32); and

identifying from the third pool one or more predominate target-binding RNA ligands that are present in the third pool at a higher concentration than other target-binding RNA ligands (for second and succeeding rounds, cDNA is sequenced to identify enriched aptamer among predominate aptamers, column 3, lines 32-36).

With regard to claim 4, Schmidt teaches a method further comprising repeating said treating, amplifying, and identifying for each subsequent pool until substantially all of the non-predominate target-binding RNA ligands in the first pool have been identified (repeating treatment, amplification and identification by sequencing to yield a detectable amount of aptamer of interest, column 3, lines 21-25 and lines 28-36).

With regard to claim 7, Schmidt teaches a method wherein each said identifying comprises:

isolating the one or more predominate target-binding RNA ligands (by separating non-complexed RNA from complexed population to enrich for the RNA aptamer of interest, whereby the non-complexed RNA will contain predominate target-binding ligands such as those binding to the blocking oligonucleotide or overlapping oligonucleotides, column 3, lines 16-17 and column 6, lines 8-24, but not those binding by shape recognition, column 5, lines 38-54) and

sequencing the one or more predominate target-binding RNA ligands (for each round of selection, cDNA is sequenced to identify enriched aptamer, column 3, lines 32-36).

With regard to claim 8, Schmidt teaches a method wherein said identifying comprises:

isolating the one or more predominate target-binding RNA ligands (by separating non-complexed RNA from complexed population to enrich for the RNA aptamer of interest, whereby the non-complexed RNA will contain predominate target-binding ligands such as those binding to the blocking oligonucleotide or overlapping

oligonucleotides, column 3, lines 16-17 and column 6, lines 8-24, but not those binding by shape recognition, column 5, lines 38-54) and

sequencing the one or more predominate target-binding RNA ligands (after first round of selection, cDNA is sequenced to identify enriched aptamer, column 3, lines 32-36).

With regard to claim 9, Schmidt teaches a method further comprising:

preparing the pool of RNA ligands that collectively bind to more than one target (contacting RNA population made from randomized DNA library, column 5, lines 22-26, with both blocking agent and selecting nucleic acid molecule, column 2, line 63 to column 3, line 15);

identifying one or more predominate target-binding RNA ligands (by separating non-complexed RNA from complexed population to enrich for the RNA aptamer of interest, whereby the non-complexed RNA will contain predominate target-binding ligands such as those binding to the blocking oligonucleotide or overlapping oligonucleotides, column 3, lines 16-17 and column 6, lines 8-24, but not those binding by shape recognition, column 5, lines 38-54).

With regard to claim 10, Schmidt teaches a method wherein said preparing comprises:

expressing a library of RNA molecules that includes both RNA ligands that bind to at least one of one or more targets and RNA molecules that do not bind any of the one or more targets (RNA population can be a randomized, synthetic RNA library, column 3, lines 26-28); and

partitioning the library of RNA molecules to form the first pool of RNA ligands (partitioning by contacting RNA population with both blocking agent and selecting nucleic acid molecule and separating non-complexed RNA from complexed population to enrich for the RNA aptamer of interest, column 2, line 63 to column 3, line 20).

With regard to claim 11, Schmidt teaches a method wherein said expressing the library of RNA molecules comprises:

expressing a library of DNA molecules that includes both DNA ligands that bind to at least one of one or more targets and DNA molecules that do not bind any of the one or more targets (random synthetic library of DNA is constructed, column 19-25); and

transcribing the library of RNA molecules from the library of DNA molecules (DNA library is transcribed into RNA population, column 25-29).

With regard to claim 14, Schmidt teaches a method wherein the targets comprise natural or synthetic small molecules, macromolecules, supramolecular assemblies, and combinations thereof (target is an RNA molecule containing selected structural element and is synthesized by transcription of synthetic DNA or cDNA, column 5, lines 9-15).

4. Claims 1, 2, 4, 7-11 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Toole et al. (U.S. Patent No. 5,582,981).

Toole teaches a method of identifying RNA ligands which bind to a target molecule (oligomer binding of target biomolecules, abstract and column 2, lines 56-64), said method comprising:

preparing, through one or more rounds of amplification and selection, a first pool of RNA ligands that collectively bind more than one target, wherein the first pool of RNA ligands comprises one or more predominate target-binding RNA ligands and one or more non-predominate target-binding RNA ligands (population used as the starting material can be a single-stranded or double-stranded RNA or DNA, column 6, lines 23-26, containing randomized sequence portion flanked by primer sequences, column 6, lines 30-36; varying degrees of randomization may be employed, column 6, lines 56-61; the synthesized pool is amplified by PCR and transcribed into RNA to provide the synthetic RNA library used in aptamer selection, and which represents a starting pool of both predominate and non-predominate target-binding RNA ligands, column 7, lines 20-24);

treating the first pool of RNA ligands under conditions effective to reduce the concentration or eliminate the presence of one or more predominate target-binding RNA ligands from the first pool of RNA ligands (contacting random oligomer population with target substance coupled to support and removing unbound members of mixture to enrich for the RNA aptamer of interest, column 2, line 65 to column 3, line 9; oligomers include RNA or DNA, column 4, lines 18-25);

amplifying the RNA ligands in the treated first pool, thereby forming a second pool of RNA ligands that is enriched in one or more non-predominate target-binding RNA ligands of the first pool but not the one or more predominate target-binding RNA ligands thereof (amplifying the recovered oligonucleotides, column 3, lines 9-10); and

identifying from the second pool one or more predominate target-binding RNA ligands that are present in the second pool at a higher concentration than other target-binding RNA ligands (sequencing the recovered and amplified oligonucleotides to identify enriched aptamer, column 3, lines 10-12).

With regard to claim 2, Toole teaches a method further comprising:

treating the second pool under conditions effective to reduce the concentration or eliminate the presence of one or more predominate target-binding RNA ligands (process is repeated a second round by contacting random oligomer population with target substance coupled to support and removing unbound members of mixture to enrich for the RNA aptamer of interest, column 2, line 65 to column 3, line 9 and column 8, lines 41-43);

amplifying the RNA ligands in the treated second pool, thereby forming a third pool of RNA ligands that is enriched in one or more non-predominate target-binding RNA ligands of the second pool but not the one or more predominate target-binding RNA ligands thereof (after the first and succeeding rounds, selected RNA population enriched for RNA aptamer of interest, is amplified, and transcribed back to RNA before next round, column 8, lines 31-43); and

identifying from the third pool one or more predominate target-binding RNA ligands that are present in the third pool at a higher concentration than other target-binding RNA ligands (after 3-6 rounds, amplified sequences can be cloned and sequenced to identify enriched ligands among predominate ligands, and to identify consensus sequences among aptamers, column 8, lines 48-58).

With regard to claim 4, Toole teaches a method further comprising repeating said treating, amplifying, and identifying for each subsequent pool until substantially all of the non-predominate target-binding RNA ligands in the first pool have been identified (repeating treatment, amplification and identification by sequencing to yield individual, distinct aptamers, column 8, lines 31-54).

With regard to claim 7, Toole teaches a method wherein each said identifying comprises:

isolating the one or more predominate target-binding RNA ligands (column 7, lines 59-67; predominate species will be the dominant species in early rounds, but will be gradually lost with each round of selection, since the specific, non-predominate species in enriched about 1,000-fold each round, column 8, lines 25-30) and

sequencing the one or more predominate target-binding RNA ligands (amplified sequences can be cloned and sequenced to identify enriched ligands among predominate ligands, column 8, lines 48-54).

With regard to claim 8, Toole teaches a method wherein said identifying comprises:

isolating the one or more predominate target-binding RNA ligands (column 7, lines 59-67; by separating unbound oligomers from complexed population to enrich for the RNA aptamer of interest among the predominate ligands, with 1,000-fold enrichment at each round, column 8, lines 25-30) and

sequencing the one or more predominate target-binding RNA ligands (amplified sequences can be cloned and sequenced to identify enriched ligands among predominate ligands, column 8, lines 48-54).

With regard to claim 9, Toole teaches a method further comprising:

preparing the pool of RNA ligands that collectively bind to more than one target (population of oligomers made from randomized sequences, column 7, lines 15-24);

identifying one or more predominate target-binding RNA ligands (amplified sequences can be cloned and sequenced to identify enriched ligands among predominate ligands, column 8, lines 48-54).

With regard to claim 10, Toole teaches a method wherein said preparing comprises:

expressing a library of RNA molecules that includes both RNA ligands that bind to at least one of one or more targets and RNA molecules that do not bind any of the one or more targets (RNA population can be made from pool of random DNA oligomers by transcription, column 7, lines 15-24); and

partitioning the library of RNA molecules to form the first pool of RNA ligands (partitioning by contacting RNA population with target coupled to solid support and separating unbound oligomers from bound population to enrich for the RNA aptamer of interest, column 7, lines 59-67).

With regard to claim 11, Toole teaches a method wherein said expressing the library of RNA molecules comprises:

expressing a library of DNA molecules that includes both DNA ligands that bind to at least one of one or more targets and DNA molecules that do not bind any of the one or more targets (pool of random DNA oligomers is generated using conventional synthesis techniques, column 7, lines 15-20); and

transcribing the library of RNA molecules from the library of DNA molecules (RNA population can be made from pool of random DNA oligomers by transcription, column 7, lines 15-24).

With regard to claim 14, Toole teaches a method wherein the targets comprise natural or synthetic small molecules, macromolecules, supramolecular assemblies, and combinations thereof (targets include polypeptides, short peptides, lipids, glycolipids, phospholipids, leukotrienes, glycoproteins, carbohydrates, or cell surface molecules, column 3, lines 58-64).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 3, 5, 6, 12, 13, 15 and 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al. (U.S. Patent No. 5,792,613) in view of Rabin et al. (U.S. Patent No. 6,344,321) as evidenced by Mugasimangalam (U.S. Patent No. 6,544,741).

Schmidt teaches the limitations of claims 1, 2, 4, 7-11 and 14 as discussed above.

With regard to claim 15, Schmidt teaches a method of reducing the concentration or eliminating the presence of unwanted target-binding species from a pool of RNA ligands, said method comprising:

providing a pool of RNA ligands which includes both wanted and unwanted target-binding RNA ligands (contacting RNA population made from randomized DNA library, column 5, lines 22-26, with both blocking agent and selecting nucleic acid molecule, column 2, line 63 to column 3, line 15);

isolating one or more unwanted target-binding RNA ligands (by separating non-complexed RNA from complexed population to enrich for the RNA aptamer of interest, whereby the non-complexed RNA will contain predominate target-binding ligands such as those binding to the blocking oligonucleotide or overlapping oligonucleotides, column

3, lines 16-17 and column 6, lines 8-24, but not those binding by shape recognition, column 5, lines 38-54);

sequencing the one or more unwanted target-binding RNA ligands (cDNA is sequenced to identify enriched aptamer, column 3, lines 32-36).

Schmidt does not teach a method of identifying RNA ligands which bind to a target molecule, comprising introducing into the pool to be treated one or more nucleic acid molecules that hybridize to the one or more predominate target-binding RNA ligands to form hybrid complexes and introducing into the pool to be treated an enzyme which cleaves at least the RNA ligand of the hybrid complexes, thereby destroying the one or more predominate target-binding RNA ligands, wherein the enzyme is RNaseH. Schmidt also does not teach a method wherein unwanted RNA ligands are bound to a nitrocellulose matrix, and are contacted with a DNA molecule to form hybrid complexes, which are destroyed upon addition of RNaseH.

With regard to claims 3, 5, 12 and 15, Rabin teaches a method wherein each said treating comprises:

introducing into the pool to be treated one or more nucleic acid molecules that hybridize to target-binding RNA ligands to form hybrid complexes (hybridization of DNA cleavage primers to RNA ligands, column 5, lines 47-55 and Figure 2, top) and

introducing into the pool to be treated an enzyme which cleaves at least the RNA ligand of the hybrid complexes, thereby removing unwanted RNA sequences (DNA:RNA hybrids are cleaved upon addition of RNaseH to remove or truncate

unwanted RNA sequences, column 15, lines 8-11 and Figure 2, bottom with cleavage sites indicated at top).

With regard to claims 6, 13, and 18, Rabin teaches a method wherein the one or more nucleic acid molecules are DNA (cleavage primers, SEQ ID Nos. 9 and 10, and Figure 2, top) and the enzyme is an RNaseH enzyme (column 5, lines 47-55 and column 15, lines 8-11).

With regard to claim 19, Rabin teaches a method wherein the one or more unwanted target-binding RNA ligands comprise one or more RNA ligands that bind to a matrix used to partition the pool of RNA ligands from a library of RNA molecules (nitrocellulose filters can be used to bind aptamers during partitioning from nucleic acids that do not interact with target, column 12, lines 13-23).

With regard to claim 20, Rabin teaches a method wherein the unwanted target-binding RNA ligands are portions of RNA ligands that bind to a matrix (fixed sequences of RNA, column 15, lines 9-10 and Figure 2, top), and wherein said treating comprises:

introducing into the pool one or more nucleic acid molecules that hybridize to the RNA ligands that bind to a matrix, thereby forming hybrid complexes (hybridization of DNA cleavage primers to RNA ligands and Figure 2, top) and

introducing into the pool an enzyme which cleaves at least portions of the RNA ligands of the hybrid complexes, thereby removing these portions of the RNA ligands that bind to a matrix (DNA:RNA hybrids are cleaved upon addition of RNaseH to remove or truncate unwanted RNA sequences, column 15, lines 8-11 and Figure 2, bottom with cleavage sites indicated at top).

With regard to claim 21, Rabin teaches a method wherein the one or more nucleic acid molecules are DNA and the enzyme is an RNaseH enzyme (cleavage primers, SEQ ID Nos. 9 and 10, and Figure 2, top) and the enzyme is an RNaseH enzyme (column 5, lines 47-55 and column 15, lines 8-11).

With regard to claim 22, Rabin teaches a method wherein the matrix is a nitrocellulose matrix (nitrocellulose filters are used to bind target molecules and target/ligand complexes for partitioning from non-binding members of the RNA mixture, column 12, lines 13-23).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Schmidt for identifying RNA ligands which bind to a target molecule with those of Rabin for selectively removing RNA sequences from a population of RNA molecules being screened as potential aptamers, since this method is highly efficient for removing specific sequences that may be unwanted in the final aptamer preparation. Thus, an ordinary practitioner would have been motivated to use methods of RNA removal as taught by Rabin since specific RNA sequences can be easily targeted for removal by designing DNA primers to remove portions of the RNA, such as for truncating fixed sequences (Rabin, column 15, lines 4-10 and Figure 2, top). Alternatively, it would also be obvious to one of ordinary skill in the art that direct removal or destruction of the aptamer sequence could be achieved by using an internal primer or primers to facilitate RNase H cleavage, as evidenced by the many examples in the literature of using primer annealing and subsequent RNase H cleavage to remove unwanted sequences from a population, such

as specific mRNA species (see Mugasimangalam, column 3, lines 44-60). The cleavage reaction using RNaseH could be performed in solution prior to partitioning (Rabin, column 15, lines 4-13) or when the aptamers are bound to nitrocellulose filters (Rabin, column 12, lines 13-23) or affinity columns (Schmidt, column column 6, lines 39-60).

Response to Arguments

8. Applicant's arguments filed July 10, 2007 have been fully considered but they are not persuasive.

Applicant argues that the 35 USC § 102(b) rejection of claims 1, 2, 4, 7-11, 14 and 15 as anticipated by Schmidt et al. (U.S. Patent No. 5,792,613) should be withdrawn since the reference no longer teaches all the limitations of the claims as amended. In particular, with regard to claim 1, Applicant argues that, although Schmidt teaches methods of preparing a first pool, the reference does not teach a subsequent step of treating the first pool of RNA ligands under conditions effective to reduce the concentration or eliminate the presence of one or more hybridizing nucleic acids from the first pool of RNA ligands. Applicant further argues that the methods of Schmidt teach a negative selection step using blocking oligonucleotides that results in a by-product that is no longer used in selection of the desired aptamer rather than deleting predominate species from the pool. The examiner asserts that the blocking step of Schmidt is performed after a step of preparation of a first pool of RNA ligands selected and produced as a randomized synthetic RNA library, rather than after a SELEX procedure. The examiner also asserts that the blocking step itself does indeed reduce

the concentration of predominant target-binding RNA ligands to enrich for the desired aptamers. The blocking oligonucleotide acts by pairing with complementary sequences in the library of potential aptamers to precude these molecules from further selection (column 2, lines 35-46). These molecules represent predominate target-binding RNA ligands because they would otherwise readily bind the selecting RNA molecule through Watson-Crick or other helix forming base interactions and prevent enrichment of those RNA molecules that bind the selecting RNA molecule through tertiary interaction (column 5, lines 38-54). Thus, the desired aptamers are separated from the more predominant target-binding species of RNA that bind by conventional base-pairing to the target sequences, and also from other bulk RNA that do not form any tertiary interactions with the target aptamers. Therefore, the 102 rejection of claim 1 and dependent claims 2, 4, 7-11 and 14 over Schmidt is maintained since this reference also teaches the subsequent amplifying and identifying steps as recited. Amended claim 15 is no longer anticipated by Schmidt, but is now included in a 103 rejection over the Schmidt and Rabin references, as discussed below.

Applicant argues that the 35 USC § 102(b) rejection of claims 1, 2, 4, 7-11, 14 and 15 as anticipated by Toole et al. (U.S. Patent No. 5,582,981) should be withdrawn since the reference no longer teaches all the limitations of the claims as amended. In particular, with regard to claim 1, Applicant argues that, although Toole teaches methods of preparing a first pool, the reference does not teach a subsequent step of treating the first pool of RNA ligands under conditions effective to reduce the concentration or eliminate the presence of one or more hybridizing nucleic acids from

the first pool of RNA ligands. Applicant argues that Toole does not teach a negative selection step as the treating step and therefore cannot teach the subsequent steps of amplifying the desired ligands and identifying the undesired ligands. The examiner asserts that the blocking step of Schmidt is performed after a step of preparation of a first pool of RNA ligands selected and produced as a randomized synthetic RNA population, rather than after a SELEX procedure. The examiner also asserts that Toole does indeed teach a method to reduce the concentration of predominant target-binding RNA ligands to enrich for the desired ligands. By incubating an oligomer mixture with a target substance coupled to a support, unbound members are removed while bound members can be recovered, amplified and sequenced to determine the complexity of the remaining selected mixture (column 2, line 65 to column 3, line 12 and column 7, line 59 to column 8, line 2), which will contain larger amounts of unwanted ligands in the earlier rounds of selection, but increasing amounts of the desired ligand in later stages of selection (enrichment up to 1000-fold at each step, column 8, lines 24-29 and 43-46). Thus, the predominate species of ligands are initially present in the pool and will be identified by sequencing analysis, but will be reduced in concentration with each round of selection. Therefore, the 102 rejection of claim 1 and dependent claims 2, 4, 7-11, and 14 over Toole is maintained. Amended claim 15 is no longer anticipated by Toole, but is now included in a 103 rejection, as discussed below.

Finally, applicant argues that the 35 USC § 103(a) rejection of claims 3, 5, 6, 12, 13 and 17-22 over Schmidt in view of Rabin (U.S. Patent No. 6,344,321) should be withdrawn since the combined references no longer teach all the limitations of the

claims as amended. Applicant argues that Rabin does not use hybridization of DNA cleavage primers to RNA ligands and subsequent RNase treatment to cleave and thus destroy unwanted RNA aptamers, but rather only to remove 5' and 3' terminal sequences from randomized aptamer sequences. Rabin teaches a method of truncate SELEX, which removes unwanted or "fixed" sequences at each selection step by hybridizing DNA oligomers and cleaving the resulting RNA/DNA complexes (column 15, lines 4-26 and Figure 2). Both predominate (unwanted) and desired sequences would be subject to cleavage, but are not immediately destroyed or otherwise removed from the population. However, the unwanted sequences are removed from the population if they fail to bind to the target in the next round of selection, thereby effectively destroying the unwanted ligand species. Alternatively, it would be obvious to one of ordinary skill in the art that direct removal or destruction of the aptamer sequence could be achieved by using an internal primer or primers to facilitate RNase H cleavage, as evidenced by the many examples in the literature of using primer annealing and subsequent RNase H cleavage to remove unwanted sequences from a population, such as specific mRNA species (see Mugasimangalam, U.S. Patent No. 6,544,741, column 3, lines 44-60). Therefore, since the teachings of Schmidt anticipate claims 1, 2, 4, 7-11 and 14 as discussed above, the 103(a) rejection of claims 3, 5, 6, 12, 13 and 18-22 over Schmidt in view of Rabin is maintained.

Conclusion

9. Claims 1-15 and 18-22 are rejected. No claims are allowable.

Correspondence

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David C. Thomas
9/7/07
Patent Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER
9/7/07